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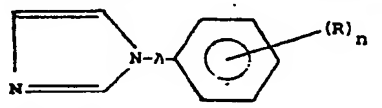
(54) Imidazole derivatives and salts thereof, their synthesis, and intermediates, and pharmaceutical formulations.

(57) The invention relates to 1-arylalkylimidazoles of formula



(I)

in which A is a straight or branched alkylene group of from 1 to 3 carbon atoms, or a straight or branched alkenylene or alkynylene group of 2 or 3 carbon atoms, n is an integer which is at least 1, and the or each R substituent, which when n is greater than 1 may be the same or different, is a saturated alkyl group of from 1 to 4 carbon atoms or an unsaturated alkyl group of from 2 to 4 carbon atoms, with the proviso that when A is unsaturated, R may also be alkoxy of from 1 to 4 carbon atoms; (when n is at least 2) alkylenedioxy of from 1 to 4 carbon atoms; halo; trihalomethyl; hydroxy; carboxyl; a salt of such a carboxyl group; carboalkoxy; carboaryloxy; carboarylalkyloxy; $-NR^6R^7$ or $-CONR^6R^7$, in which R^6 and R^7 may be the same or different and are hydrogen or alkyl of from 1 to 4 carbon atoms; or an acid addition salt of such a 1-arylalkylimidazole.

Methods of preparing these 1-arylalkylimidazoles are disclosed.

The 1-arylalkylimidazoles have pharmacological properties of use in medicine, in particular for the treatment of prophylaxis of thrombo-embolic disorders.

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Imidazole derivatives and salts thereof, their synthesis and intermediates, and pharmaceutical formulations.

The present invention relates to imidazole derivatives and salts thereof, to their synthesis and intermediates therefor, to pharmaceutical formulations containing such compounds and to the use of these compounds in medicine.

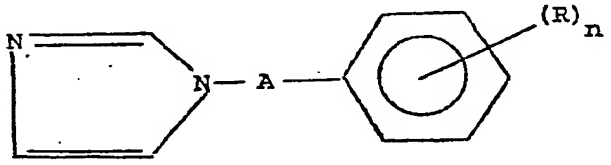
Thromboxane A_2 (TXA_2), a potent stimulator of blood platelet aggregation, is produced, in platelets, from the prostaglandin endoperoxides PGG_2 and PGH_2. Prostacyclin (PGI_2), which has potent anti-aggregatory activity, is also produced (in blood vessel wals) from PGG_2 and PGH_2 and it has been suggested that a balance between the production of TXA_2 and PGI_2 is the controlling factor in thrombus formation. It would, in consequence be desirable in the treatment and prophylaxis of thrombo-embolic disorders to be able to selectively inhibit TXA_2 synthetase, thereby favouring the production of the anti-aggregatory agent PGI_2.

Imidazole and 1-methylimidazole are known to provide some degree of inhibition of the enzymic conversion of the endoperoxides (PGG_2 and PGH_2) to thromboxane A_2 by platelet microsomes (Moncada et al., Prostaglandins, 13/4, 611-618. 1977). Certain 1-n-

alkylimidazoles, especially 1-n-dodecylimidazole and its higher homologues have been described as being capable of lowering serum cholesterol levels (U.K. Patent No. 1 364 312; Biochem. Pharmacol. 24, 1902-1903, 1975).

We have now discovered that TXA_2 synthetase may be inhibited by 1-arylalkylimidazoles of formula (I) and acid addition salts thereof. The compounds of formula (I) and their salts are hereinafter referred to as the "active compounds".

The compounds of formula (I) are novel and of formula:



(I)

in which A is a straight or branched alkylene group of from 1 to 3 carbon atoms, or a straight or branched alkenylene or alkynylene group of 2 or 3 carbon atoms, n is an integer which is at least 1, and the or each R substituent, which when n is greater than 1 may be the same or different, is a saturated hydrocarbon group of from 1 to 4 carbon atoms, or an unsaturated hydrocarbon group of from 2 to 4 carbon atoms with the provisos that

(a) when A is a methylene or ethylidine group, n is at least 2 when R is a saturated hydrocarbon group,

(b) when A is a branched propylene, or straight propylidene group, n is at least 3 when R is a saturated hydrocarbon group,

(c) when A is unsaturated R may also be selected from alkoxy of from 1 to 4 carbon atoms; alkylenedioxy of from 1 to 4 carbon atoms, when n is at least 2; halo; trihalomethyl; hydroxy; carboxyl; a salt of such a carboxyl group; carboalkoxy; carboaryloxy; carboaryl-alkyloxy; $-NR^6R^7$ or $-CONR^6R^7$, in which R^6 and R^7 may be the same or different and are hydrogen or alkyl of from 1 to 4 carbon atoms; with the further proviso that when n is 1, R is not a saturated hydrocarbon group;

or an acid additon salt of such a 1-arylalkylimidazole.

In formula (I) examples of the group A are:-

methylene,

propylene, and,

in the orientation of formula (I),

$-CH_2-CH=CH-$, (cis or trans or isomeric mixture thereof).

A valuable class of compounds of formula (I) are those in which the aromatic ring is substituted by at least two saturated or unsaturated alkyl radicals, especially if one substituent is in the 4-position in the benzene ring and A is either methylene ($-CH_2-$) or, in the orientation of formula (I), $-CH_2-CH=CH-$ (cis or trans or a cis/trans mixture-cinnamyl compounds). When A is unsaturated, preferred compounds are those in which the aromatic ring contains alkyl, chloro or methoxy substituents.

Compounds of formula (I) may also be used as acid addition salts thereof, especially as pharmaceutically acceptable ones.

Especially preferred compounds include:-

1-(3,4-dimethylbenzyl)imidazole

1-(2,4-dichlorocinnamyl)imidazole i.e. 1-[3-(2,4-dichlorophenyl) prop-2-enyl]imidazole

1-[3-(2,6-dichlorophenyl)prop-2-enyl]imidazole, and acid addition salts thereof.

Other preferred compounds include:-

1-(2,4,6-trimethylbenzyl)imidazole

1-[3-(3,4,5-trimethoxyphenyl)prop-2-enyl]imidazole

1-[3-(3,4-dimethoxyphenyl)prop-2-enyl] imidazole

1-[3-(2-hydroxyphenyl)prop-2-enyl]imidazole

1-[3-(3-bromophenyl)prop-2-enyl]imidazole

1-[3-(4-chlorophenyl) prop-2-enyl] imidazole

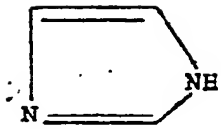
1-[3-(3,4-dimethylphenyl) prop-2-enyl]imidazole

1-[3-(2-methoxyphenyl)prop-2-enyl]imidazole, and acid addition salts thereof.

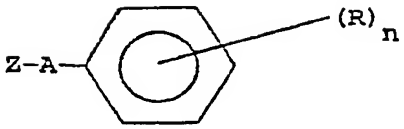
In contrast to imidazole and 1-methylimidazole, the compounds of formula (I) are more potent inhibitors of TXA_2 synthetase. Many of the compounds (for example in formula (I) R is 3,4-dimethyl and A is $-CH_2-$ or in the orientation of formula (I), $-CH_2CH=CH-$) are also more selective in their action in not inhibiting other anti-aggregatory prostaglandin-generating enzymes. The compounds of formula (I) also do not produce the side-effects found with imidazole upon in vivo administration. The compounds of formula (I) are further capable of inhibiting platelet aggregation in vivo and also are capable of disaggregating platelet clumps, the compounds 1-(3,4-dimethylbenzyl)imidazole, 1-(2,4-dichlorocinnamyl)imidazole and 1-(2,6-dichlorocinnamyl)imidazole, and their salts especially displaying these properties.

Imidazoles of formula (I) and acid addition salts thereof may be made by any method known in the art for the synthesis of compounds of analogous structure. In general these methods comprise linking the imidazole ring to the remainder of the molecule; converting a precursor molecule by elimination of a functional group; and formation of the desired compound from a corresponding pyrazole, imidazoline or other unsaturated analogue.

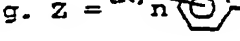
A most convenient method of synthesis involves the reaction of imidazole (formula (II) or a salt thereof with an arylalkylating agent of formula (III):



(II)

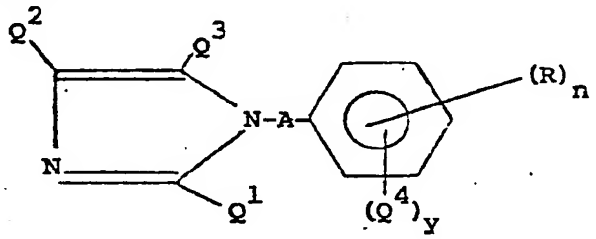


(III)

wherein R, n, and A are as defined in formula (I) and Z is a leaving group. This reaction is well established in the literature, and the leaving group may be chosen from a variety of substituents but especially halo, preferably chloro or bromo, or from p-toluenesulphonyloxy but other arylsulphonyloxy, alkanesulphonyloxy or arylalkylsulphonyloxy radicals may be used. The reaction is preferably performed in the presence of an acid acceptor, for example an alkali metal alkoxide, such as sodium methoxide or potassium tertiary butoxide, in the presence of an alkanol. The leaving group Z may itself be formed in situ from the corresponding alkanol (Z = OH) by reaction with a hydrohalogenic acid (e.g. hydrochloric acid or a Lewis acid, such as aluminium chloride: see Japanese Patent Kokai No. 131577/77) and the resulting agent of formula (III) reacted directly with imidazole without prior isolation. Alternatively an alkanol (Z = OH) or a derivative thereof (e.g. Z = ) may be reacted directly with

imidazole (II) by heating in the presence of a dehydrating agent, such as phosphoric acid, or a phosphate (see Japanese Patent Publication No. 51 105 060), sulphuric acid or sulphates (see Japanese Patent Publication No. 51 105 061).

Among precursor molecules which may be converted to a compound of formula (I) or an acid addition salt thereof, are substituted imidazole derivatives of formula (IV) or addition salts thereof.

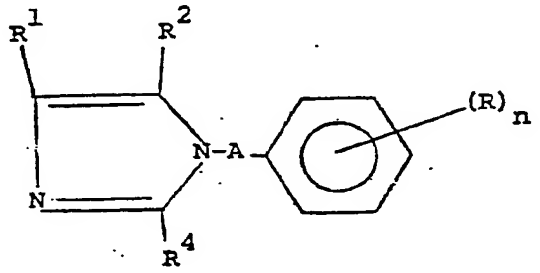


(IV)

wherein A, n and R are as defined in formula (I), and Q^1, Q^2, Q^3 and Q^4 are the same or different, at least one being a radical capable of removal by, for example reduction or oxidation, the remaining radical or radicals being selected from hydrogen or a radical capable of removal in the same or another manner (e.g. a carboxyl group -see formula (VI)-removed by decarboxylation), y is 0 or an integer with the proviso that y and n together do not exceed 5. Q^1, Q^2, Q^3 and Q^4 may be selected for example from thio (-SH), alkylthio (-S-alkyl, wherein alkyl has from 1 to 4 carbon atoms) or halo preferably chloro or bromo. The reaction conditions are chosen according to the nature of the radicals Q^1, Q^2, Q^3 and Q^4. Desulphurisation may be performed by oxidative or reductive procedures using for example nitric acid or Raney

nickel; and reductive dehalogenation by the use of zinc and acetic acid or Raney nickel or other reagents known in the art or described in the literature.

Another class of examples include carboxyimidazoles or derivatives thereof of formula (VI);



(VI)

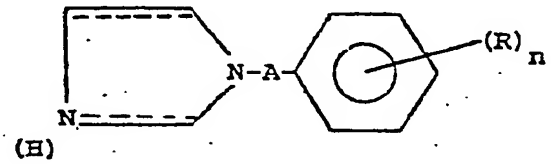
wherein A, n, and R are as defined in formula (I), at least one of R^1, R^2 and R^4 is carboxyl or a derivative thereof (for example an ester such as an alkyl ester, an acid halide such as the chloride, or the nitrile) and the other(s) is hydrogen or carboxyl or a derivative as described. The compounds of formula (VI) may be converted into the imidazoles of formula (I) by any suitable decarboxylation conditions which may simply comprise heating the compounds with or without a catalyst, such as copper.

The imidazoles of formula (I) may also be made from a compound of formula (VII):

(VII)

wherein N is 1-imidazoline, 1-imidazole or 1-pyrazole, A^1 is straight or branched saturated or unsaturated acyclic

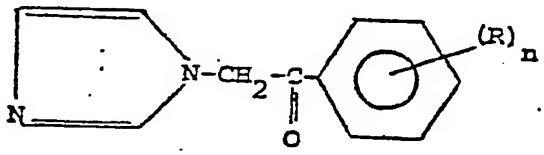
hydrocarbon radical which may include a keto-group, and R^3 is  wherein R and n are as defined in formula (I) and when A is unsaturated R may also be nitro provided that at least one of  , A^1 and R^3 is other than 1-imidazole, a saturated acyclic hydrocarbon group and  as defined in formula (I). Thus an imidazoline (VIII):



(VIII)

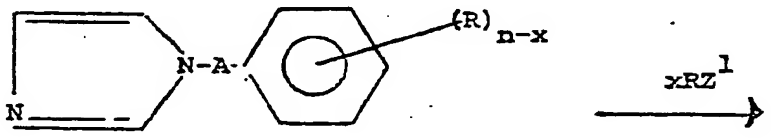
wherein one of -----represents an extra bond, and A, n and R are as defined in formula (I), may be dehydrogenated to the corresponding imidazole in the presence of a catalyst, for example by heating to 250°C in the presence of palladium, nickel or platimun under pressure, or by heating with a dehydrogenating agent, such as selenium or copper oxide. 1-Pyrazole compounds (VII) may be treated with ultra-violet irradiation, optionally under an inert atmosphere (e.g. argon) in for example 1,2-dimethoxyethane at room or elevated temperatures (see for example "Ring Transformations of Heterocycles" edited van der Plas, Academic Press, 1973 at page 261). The unsaturated imidazoles of formula (I) (in formula (VII), A^1 and/or R (within R^3) are unsaturated) may be reduced to corresponding less saturated or completely saturated compounds (but not reducing the aromatic nucleus) with a noble metal catalyst for example platinum or palladium in an alkanol. If R is amino in the final product then its precusor may be a nitrogen-containing group reducible to

amino e.g. nitro. A compound for example of formula

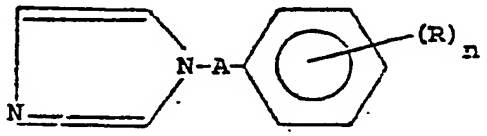


(IX)

where R and n are as for formula (I), may be reduced at the keto group to a $-CH_2-$ group for example by a Clemmensen reduction. Where one or more of the R groups is a saturated or unsaturated alkyl group it may be introduced into the phenyl ring by a Friedel Crafts or similar Lewis-acid catalysed reaction of the type.



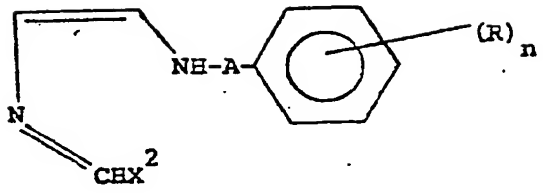
(X)



(I)

wherein A, R and n are as defined for formula (I), x is an integer less than or equal to n and Z^1 is a leaving group, e.g. halo, suitable for use in this type of alkylation.

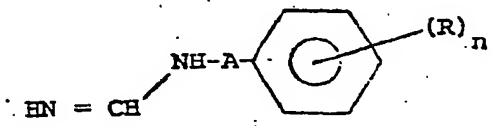
Compounds of formula (I) may also be prepared by cyclising preferably in the presence of an acid acceptor, a compound of formula



(XI)

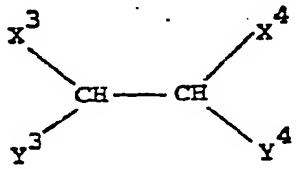
wherein A, R and n are as defined for formula (I) and X^2 is a leaving group.

Compounds of formula (I) may also be prepared by reacting a compound of formula



(XII)

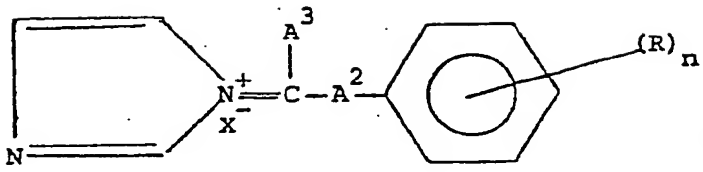
wherein A, R and n are as defined for formula (I), with a compound of formula:



(XIII)

wherein either of X^3 and Y^3 is a leaving group such as halo or hydroxy and the other is hydrogen, or X^3 and Y^3 are both halo or together form a keto group or an acetal derivative thereof e.g. both X^3 and Y^3 are alkoxy, and X^4 and Y^4 are as defined for X^3 and Y^3, although they may be the same as or different from X^3 and Y^3.

An imine salt of for example formula

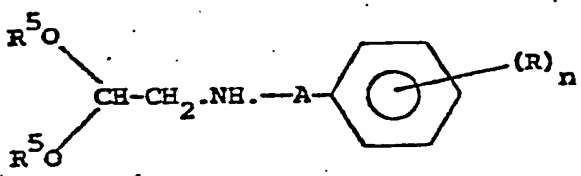


(XIIIa)

(wherein R and n are as for formula I, X^- is an anion, A^2 is a chemical bond or a straight or branching saturated or unsaturated acyclic hydrocarbon radical, which may include a keto group, A^3 is hydrogen or a saturated or unsaturated acyclic hydrocarbon radical, which may include a keto group, with the proviso that A^2 and A^3 together contain no more than 2 carbon atoms) may be reduced to the corresponding compound of formula (I), by e.g. zinc and a mineral acid, e.g. hydrochloric acid.

The intermediates for use in the above described reactions may also be made by conventional methods known in the art. Thus the 1-pyrazole and 1-imidazoline intermediates (formula (VII)) may be prepared by alkylation of pyrazole and imidazoline in an analogous manner to that described above for preparation of the corresponding imidazoles. The intermediates of formula (III) may be made in known manner preferably by halogenation of the corresponding alcohols (formula (III), Z = -OH) where A is unsaturated in such compounds the alcohol is conveniently prepared from paraformaldehyde and a precursor molecule with an unsaturated A group containing two

carbon atoms (cf Bull. Chem. Soc. Japan, 46/8, 2512-5, 1973). The substituted imidazole intermediates of formula (IV) may be made in known manner, for example see "Imidazole and its derivatives" Part I, Ed. K. Hofmann, Interscience Publishers Inc. New York, 1973. For example the 2-thioimidazoles of formula (IV) may be made by cyclisation of an acetal of formula (XIV):



(XIV)

with thiocyanate, wherein R^5 is alkyl, aryl or arylalkyl.

The pharmaceutically acceptable addition salts of the compounds of formula (I) may be prepared by any method known in the art. In particular they may be prepared by treating the parent imidazole with the appropriate acid.

Examples of the addition salts of the compounds of formula (I) include those salts derived from the following acids: oxalic, hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic.

The imidazoles of formula (I) may be used in conjunction with a phosphodiesterase inhibitor, which provides a further

synergistic increase in effect, as it acts against platelet aggregation by a different pathway.

Suitable phosphodiesterase inhibitors for use in potentiating the anti-aggregatory effects of the active compounds include as such or as pharmaceutically acceptable salts:-

(a) Xanthine derivatives such as:-

Theophylline(3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione), and salts thereof;

3-Isobutyl-1-methyl-xanthine;

Coffeine(3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) and salts thereof, and

Aminophylline (adduct of Theophylline and 1,2-ethanediamine (2:1)).

(b) Isoquinoline derivatives, for example:-

Papaverine (6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-isochinolin) and salts thereof; and

6,7-Diethoxy-1-(4.5-diethoxybenzyl)isoquinoline or its salts e.g. its hydrochloride,

(c) Derivatives of pyrimido(5,4-d-pyrimidine, for example:-

Dipyridamole(2,2',2"'-(4,8-dipiperidino-pyrimido [5,4-d]pyrimidin-2,6-diyldinitrilo-tetraethanol) and its salts;

2,2',2"'-[[4-(1-piperidinyl)pyrimido[5,4-d] pyrimidin-2,6-diyl]dinitrilo]tetrakisethanol and its salts; and

2,4,6-tri-4-morpholinylpyrimido[5,4-d]pyrimidine and its salts.

(d) Derivatives of thieno[3,2-d]pyrimidine,for example:-

N-[4-(4-morpholinyl)thieno[3,2-d]pyrimidin-2-yl]-1,2-ethanediamine.

(e) Derivatives of pyrazolo[3',4':2,3]pyrido[4,5-b][1,5]benzodiazepin-6-(3H)-one, for example:-

3-Ethyl-7,12-dihydro-7,12-dimethylpyrazolo-[4',3':5,6]pyrido[4,3-b][1,5]-benzodiazepin-6(3H)-one;

10-Chloro-3-ethyl-7,12-dimethyl-7,12-dihydro-pyrazolo[4',3':5,6]pyrido[4,3-b][1,5]benzo-diazepin-6-(3H)-one.

(f) Derivatives of 1H- or 2H-pyrazolo[3,4-b]-pyridine, for example:-

4-(Butylamino)-1-ethyl-1H-pyrazolo[3,4-b]-pyridine-5-carboxylic acid ethyl ester.

4-(Butylamino)-1H-pyrazolo[3,4-b]pyridine-6-carboxylic acid ethyl ester;

4-Chloro-1-ethyl-3-methyl-1H-pyrazolo[3,4-b]-pyridine-5-acetonitrile;

1-Ethyl-4-(isopropylidenehydrazino)-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester or its salts such as its hydrochloride hemihydrate; and

2-Methyl-6-phenyl-4-(1-piperidinyl)-2H-pyrazolo-[3,4-b]pyridine or its salts e.g. its hydrochloride.

(g) Derivatives of 5H-furo[3,4-e]pyrazolo[3,4-b]pyridine-5-one, for example:-

4-(Butylamino)-1-ethyl-1,7-dihydro-7-hydroxy-5H-furo-[3,4-e]pyrazolo[3,4-b]pyridine-5-one; and

(h) Derivatives of 1(2H)-naphthalenone, for example:-

2-[(Dimethylamino)methyl]-3,4-dihydro-7-methoxy-1(2H)-naphthalenone or its salts e.g. its 1:1 hydrochloride.

The active compounds are particularly useful in the treatment and/or prophylaxis of thrombo-embolic disorders in mammals, including man. It is to be understood that the term "thrombo-embolic disorders" includes those disorders whose etiology is associated with platelet aggregation.

The active compounds are useful wherever it is desired to inhibit platelet aggregation and/or to reduce the adhesive character of platelets, and consequently to treat or prevent the formation of thrombi in mammals, including man. For example, the compounds are useful in the treatment and prevention of myocardial infarcts, cerebro-vascular thrombosis and ischaemic peripheral vascular disease; to treat and prevent post-operative thrombosis; and to promote patency of vascular grafts following surgery.

The active compounds are also useful as an addition to blood, blood products, blood substitutes, and other fluids which are used in artificial extra-corporeal circulation and perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant,,or attached to a new body. It may also be used in laboratory animals, e.g. cats, dogs, rabbits, monkeys and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

The active compounds also exhibit some vasodilatory action on blood vessels and therefore have a utility as anti-hypertensives for the treatment of high blood pressure in mammals, including man.

The amount of active compound required for therapeutic or prophylactic effect will vary with the route of administration,

and the nature of the condition under treatment. In general a suitable dose for a mammal, including man, of active compound will lie in the range of 0.1 to 300 mg per kg body weight, particularly from 0.5 to 10 mg per kg body weight, for example 2 mg per kg. A suitable single oral dose for an adult human lies within the range of 50 to 600 mg, for example 150 mg given say three times a day.

While it is possible for the active compounds to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. The formulations, both for veterinary and for human medical use, of the present invention comprise an active compound as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be 'acceptable' in the sence of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Unit doses of a formulation may contain between 60 mg and 1.5 g of an active compound.

The formulations include those suitable for oral, rectal, vaginal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred formulations include tablets, capsules and injectable suspensions or solutions.

The formulations may conveniently be presented in unit dosage from and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of

bringing into association the active compound (in the form of the base or a pharmaceutically acceptable acid addition salt) with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

It will be appreciated from the foregoing that the present invention provides the following features:-

(a) Novel 1-arylalkylimidazoles of formula (I), and acid addition salts thereof.

(b) Methods of preparing imidazoles of formula (I) and acid addition salts thereof.

(c) Pharmaceutical formulations containing the imidazoles of formula (I) or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

(d) Method of preparing the pharmaceutical formulations containing the imidazoles of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

(e) A method for the treatment or prophylaxis of a thrombo-embolic disorder in a mammal or mammalian tissue, including man or human tissue, comprising administering an active compound.

(f) An 1-arylalkylimidazole of formula (I) or salt thereof as an active agent for the treatment of a thrombo-embolic disorder in a mammal or mammalian tissue, including man or human tissue.

The following Examples are provided by way of an illustration of the present invention and should in no way be construed as constituting a limitation thereof. All temperatures are given in degrees Celsius.

EXAMPLE 1

Preparation of 1-(3,4-Dimethylbenzyl)imidazole

1-Chloromethyl-3,4-dimethylbenzene (34.76 g, 0.225 mol) was added to a mixture of imidazole (13.6 g, 0.2 mol) and sodium bicarbonate (16.8 g, 0.2 mol) in dry methanol (100 ml). Following the addition, the reaction mixture was stirred and heated under reflux for 3 h.

After cooling, the reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to afford a yellow oil. The residue was extracted with chloroform (3 x 100 ml), and the combined extracts were washed with saturated brine (100 ml). The chloroform solution was dried over magnesium sulphate, and then concentrated under reduced pressure. The resulting oil was purified using a silica gel column and ethyl acetate/methanol (9:1) as eluent. The product fractions were pooled, concentrated, and the resulting oil was distilled to afford 1-(3,4-dimethylbenzyl)imidazole b.p. 128-130°/0.3mm Hg.

EXAMPLE 2 - Salts of 1-(3,4-Dimethylbenzyl)imidazole

A. Hydrogen Fumarate

A solution of fumaric acid (0.29 g, 0.0025 mol) in hot ethanol (10 ml) was added to a stirred solution of 1-(3,4-dimethylbenzyl)imidazole (0.46 g, 0.0025 mol) in hot ethanol (10 ml). After boiling for 0.25 h, the solution was evaporated to afford a white solid. Recrystallisation of the solid from

ethyl acetate afforded 1-(3,4-dimethylbenzyl)imidazole hydrogen fumarate 1/6 hydrate as a white solid m.p. 138-140°.

B. Hydrogen Succinate

A hot solution of succinic acid (0.295 g, 0.0025 mol) in hot ethanol (20 ml) was added to a stirred, hot solution of 1-(3,4-dimethylbenzyl)imidazole (0.46 g, 0.0025 mol) in hot ethanol (10 ml). After boiling for 0.25 h, the solution was evaporated under reduced pressure to afford a white solid. Recrystallisation of the solid from ethyl acetate/petroleum ether (b.p. 40-60°) afforded 1-(3,4-dimethylbenzyl)imidazole hydrogen succinate as white crystals, m.p. 134-135°.

C. Hydrogen Oxalate

A hot solution of oxalic acid (0.225 g, 0.0025 mol) in dry ethanol (10 ml) was added to a solution of 1-(3,4-dimethylbenzyl) imidazole (0.46 g, 0.0025 mol) in hot ethanol (20 ml). After boiling for 0.25 h, the solution was evaporated to afford a white solid. Recrystallisation of the solid from ethanol/petroleum ether (b.p. 40-60°) afforded 1-(3,4-dimethylbenzyl)imidazole hydrogen oxalate as a white solid, m.p. 92-93°.

EXAMPLE 3

Preparation of 1-[3-(2,4-Dichlorophenyl)prop-2-enyl]imidazole

1-Chloro-3-(2,4-dichlorophenyl)prop-2-ene (11.1 g, 0.05 mol) was added dropwise to a stirred solution of imidazole (3.4 g, 0.05 mol) and potassium tert-butoxide (5.6 g, 0.05 mol) in

butan-1-ol (100 ml). Following the addition, the reaction mixture was stirred and heated under reflux for 3.5 h.

After cooling, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Hydrochloric acid (150 ml, 2M) was then added to the residue and the aqueuos mixture was washed with ether (1 x 60 ml). The acidic solution was then basified with sodium hydroxide solution (10M) and the resulting oil was extracted with chloroform. The chloroform extracts were combined and dried over magnesium sulphate. Evaporation of the chloroform under reduced pressure afforded a pale yellow oil which was purified using a silica gel column and by elution with ethyl acetate/methanol (9:1). The product fractions were pooled and concentrated to afford an oil which was distilled, to afford 1-[3-(2,4-dichlorophenyl) prop-2-enyl]imidazole, b.p. 144-148°/0.007 mmHg.

EXAMPLE 4

Preparation of 1-[3-(2,6-Dichlorophenyl)prop-2-enyl]imidazole

1-Chloro-3-(2,6-Dichlorophenyl)prop-2-ene (11.1 g, 0.05 mol) was added dropwise to a stirred solution of imidazole (3.4 g, 0.05 mol) and potassium tert-butoxide (5.6 g, 0.05 mol) in butan-1-ol (100 ml). Following the addition, the reaction mixture was stirred and heated under reflux for 3.5 h.

After cooling, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Hydrochloric

acid (150 ml, 2M) was then added to the residue, and the aqueous mixture was washed with ether (1 x 60 ml). The acidic solution was then basified with sodium hydroxide solution (10M), and the resulting oil was extracted with chloroform. The chloroform extracts were combined and dried over magnesium sulphate. Evaporation of the chloroform under reduced pressure afforded a pale yellow oil which was purified using a silica gel column and by elution with ethyl acetate/methanol (9:1). The product fractions were pooled and concentrated to afford an oil which was distilled, to afford 1-[3-(2,6-dichlorophenyl)-prop-2-enyl]imidazole, b.p. 156-158°/0.02 mmHg.

EXAMPLE 5

Biological Results

Horse platelets were prepared from whole horse blood by differential centrifugation. Approximately 10^6 platelets were homogenised in 1 ml 100 mM Tris buffer pH 7.4. Various concentrations of active compound were added and the reaction sets incubated for 5 minutes at ambient temperature. To each tube was added 20 nM of arachidonic acid containing 10^6 disintegrations per minute (DPM) of labelled arachidonic acid and the tubes incubated for 3 minutes at 37°C in a shaking water bath. After incubation the radioactive products were extracted from the acidified aqueous phase with ethyl acetate and after concentration resolved by thin-layer chromotography on silica gel with chloroform/methanol/acetic acid/water

(90:8:1:0.8) as a developing solvent. The amount of thromboxane produced was measured by scraping the radioactive zone corresponding to thromboxane B_2 and estimating the radioactivity in a liquid scintillation counter.

The concentration of active compound to reduce the enzyme activity by 50% (ED_{50}) was established. The results are shown in Table A.

The selectivity of the active compounds was measured in a similar manner to that described above and the amount of PGE, PGF and PGD produced was determined. The greater the selectivity, the more of the anti-aggregating prostaglandins are produced.

The ED_{50} and Selectivity results are shown in Table A in which O indicates no selectivity; + low selectivity: ++ medium selectivity; +++ high selectivity, and ++++ exceptionally high selectivity.

TABLE A

Compound (Reference Compound)	ED_{50} µg/ml	Selectivity
(Imidazole)	⩾500	O to +
(1-Methylimidazole)	⩾200	++
1-(3,4-dimethylbenzyl)imidazole	6	++
1-[3-(2,4-dichlorophenyl)prop-2-enyl]imidazole	4.1	+
1-[3-(2,6-dichlorophenyl)prop-2-enyl]imidazole	1	+

EXAMPLE 6

Tablet formulation

1-(3,4-dimethylbenzyl)imidazole (as a salt)	150 mg
Starch	25 mg
Polyvinylpyrrolidone	2 mg
Magnesium stearate	3 mg

The imidazole salt is ground to a fine powder, blended with the starch and then the mixture granulated with an aqueous solution of the polyvinylpyrrolidone. The granules are sieved 1000 μ, dried, sieved again and the magnesium stearate added. The mixture is then compressed into tablets.

In the same manner, tablets of 1-[3-(2,4-dichlorophenyl)-prop-2-enyl]imidazole and 1-[3-(2,6-dichlorophenyl)prop-2-enyl] imidazole are prepared.

EXAMPLE 7

Tablet formulation

Tablets (150 mg) of the imidazoles described in the preceding example 6 are prepared in the same manner from the following ingredients:-

The Imidazole Compound (as a salt)	150 mg
Lactose	100 mg
Starch	30 mg
Polyvinylpyrrolidone	2 mg
Magnesium stearate	3 mg

In the preparation, the lactose is blended with the starch.

EXAMPLE 8

Tablet formulation

Tablets (100 mg) of the imidazoles of Example 6 are prepared in the same manner from the following ingredients:

The Imidazole Compound (as a salt)	100 mg
Sodium starch glycollate	10 mg
Polyvinylpyrrolidone	2 mg
Magnesium stearate	3 mg

EXAMPLE 9

Tablet formulation

Tablets (150 mg) of the imidazoles of Example 6 are prepared in the same manner from the following ingredients, except that the starch, pregelled starch and imidazole compound are all blended together prior to granulation:-

The Imidazole Compound (as a salt)	150 mg
Starch	25 mg
Pregelled starch	5 mg
Magnesium stearate	3 mg

EXAMPLE 10

Injectable formulation

Imidazole compound of formula (I)	15.0 g
Lactic Acid B.P.*	q.s.** to pH 3.0
Water for Injections B.P.**	to 100.0 ml

Suspend the compound in 3/4 of the available quantity of water. Add sufficient lactic acid to dissolve the compound and to reduce the pH to 3.0. Dilute to volume with Water for Injections.

Sterilise the solution by passage through a membrane filter, pore size 0.22 µm.

Distribute the solution using aseptic precautions into sterilised ampoules, 1 ml per ampoule. Seal by fusion of the glass.

Each 1 ml ampoule supplies 150 mg of the imidazole compound: 1-(3,4-dimethylbenzyl)imidazole hydrogen fumarate.

EXAMPLE 11

Injectable formulation

Imidazole compound of formula (I)	15.0 g
Citric Acid B.P.	q.s. to pH 3.0
Chlorocresol	0.1 g
Water for Injections to	100.0 ml

Suspend the compound in ¾ the final volume of Water for Injections. Add sufficient citric acid as a 10% solution in

Water for Injections to dissolve the compound and reduce the pH to 3.0. Dilute to volume with Water for Injections.

Sterilise the solution by passage through a membrane filter, pore size 0.22 µm.

Distribute the solution with aseptic precautions into sterilised vials, 25 ml per vial. Stopper with sterile rubber closures and seal with an aluminium cap.

Each 1 ml of solution provides 150 mg of the compound: 1-(3,4-dimethylbenzyl)imidazole hydrogen fumarate.

EXAMPLE 12

Injectable formulation

In the manner described in the preceding two Examples, injectable formulations of 1-[3-(2,4-dichlorophenyl)prop-2-enyl]imidazole and 1-[3-(2,6-dichlorophenyl)prop-2-enyl] imidazole salts were prepared.

EXAMPLE 13

By the method described in Example 1 above the following compounds were prepared:-

(a) 1-(2,4,6-trimethylbenzyl)imidazole

(b) 1-[3-(3,4,5-trimethoxyphenyl)prop-2-enyl]imidazole

(c) 1-[3-(3,4-dimethoxyphenyl)prop-2-enyl]imidazole

(d) 1-[3-(2-hydroxyphenyl)prop-2-enyl]imidazole

(e) 1-[3-(3-bromophenyl)prop-2-enyl]imidazole

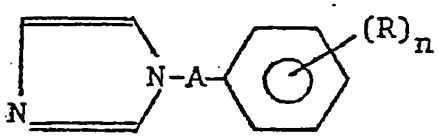
(f) 1-[3-(4-chlorophenyl)prop-2-enyl]imidazole

(g) 1-[3-(3,4-dimethylphenyl)prop-2-enyl]imidazole

(h) 1-[3-(2-methoxyphenyl)prop-2-enyl]imidazole

CLAIMS:

1. A 1-arylalkylimidazole characterised in that said compound has the formula:



in which A is a straight or branched alkylene group of from 1 to 3 carbon atoms, or a straight or branched alkenylene or alkynylene group of 2 or 3 carbon atoms, n is an integer which is at least 1, and the or each R substituent, which when n is greater than 1 may be the same or different, is a saturated alkyl group of from 1 to 4 carbon atoms or an unsaturated alkyl group of from 2 to 4 carbon atoms, with the provisos that

(a) when A is a methylene or ethylidene group, n is at least 2 when each R is saturated alkyl;

(b) when A is a branched propylene or straight propylidene group, n is at least 3 when each R is saturated alkyl;

(c) when A is unsaturated R may also be selected from alkoxy of from 1 to 4 carbon atoms; when n is at least 2, alkylenedioxy of from 1 to 4 carbon atoms; halo; trihalomethyl; hydroxy; carboxyl; a salt of such a carboxyl group; carboalkoxy; carboaryloxy; carboarylalkyloxy; $-NR^6R^7$ or $-CONR^6R^7$, in which R^6 and R^7 may be the same or different and are hydrogen or alkyl of from 1 to 4 carbon atoms; with the further proviso that when n is 1, R is not a saturated alkyl group;

or an acid addition salt of such a 1-arylalkylimidazole.

2. A 1-arylalkylimidazole as defined in claim 1 characterised in that A is $-CH_2-$ or, in the orientation of formula (I), $-CH_2-CH=CH-$.

3. A 1-arylalkylimidazole as defined in claim 2 characterised in that R and n together are 3,4-dimethyl substituents in the phenyl ring.

4. A 1-arylalkylimidazole characterised in that it is selected from 1-(3,4-dimethylbenzyl) imidazole, 1-[3-(2,4-dichlorophenyl)prop-2-enyl] imidazole, and 1-[3-(2,6-dichlorophenyl)prop-2-enyl] imidazole and acid addition salts thereof.

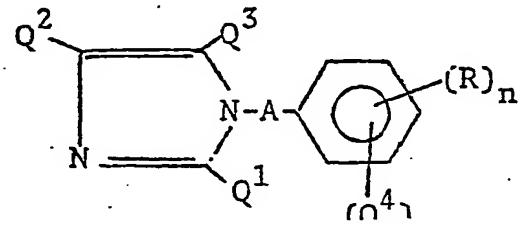
5. 1-(3,4-dimethylbenzyl)imidazole or an acid addition salt thereof.

6. 1-(3,4-dimethylbenzyl)imidazole.

7. A method of preparing a 1-arylalkylimidazole or an acid addition salt thereof as defined in claim 1 characterised in that one reacts imidazole or a salt thereof with an alkylating agent of the formula Z-A-  $_n$ wherein A, n and R are as defined in claim 1 and Z is a leaving group.

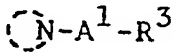
8. A method of preparing a 1-arylalkylimidazole of the formula defined in any of claims 1 to 6 or an acid addition salt thereof characterised in that one

(a) converts a substituted imidazole of the formula:



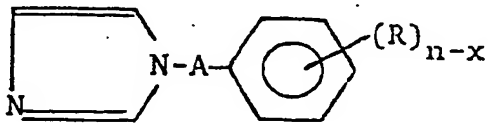
wherein A, n and R are defined in formula (I) and Q^1, Q^2, Q^3 and Q^4 are the same or different, at least one being a radical capable of removal, the other(s) being a radical having the same or other removable function or is hydrogen, y is 0 or an integer, with the proviso that y and n together do not exceed 5;

(b) converts a precursor of the formula



wherein is 1-imidazoline, 1-imidazole or 1-pyrazole, A^1 is a straight or branched, saturated or unsaturated acyclic hydrocarbon radical which may include a keto group, and R^3 is as defined in formula (I) and R may also be nitro if A is unsaturated, provided that at least one of  , A^1 and R^3 is other than 1-imidazole, a saturated acyclic hydrocarbon group and  as defined in formula (I);

(c) alkylates a compound of formula (X):

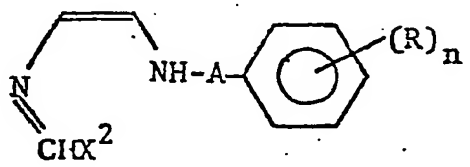


(X)

wherein A, R and n are as defined for formula (I) and x is an integer less than or equal to n with

a compound of formula RZ^1 wherein R is an alkyl group as defined for formula (I) and Z^1 is a leaving group;

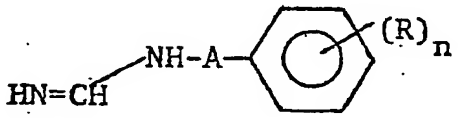
(d) cyclises a compound of formula (XI):



(XI)

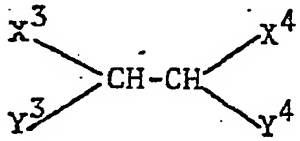
wherein A, R and n are as defined for formula (I) and X^2 is a leaving group;

(e) reacts a compound of formula (XII):



(XII)

wherein A, R and n are as defined for formula (I) with a compound of formula (XIII):

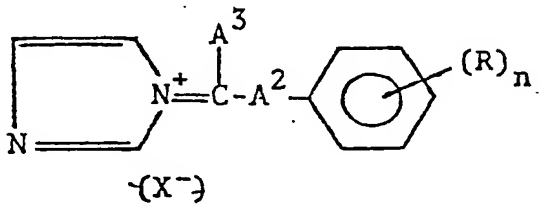


(XIII)

wherein either of X^3 and Y^3 is a leaving group and the other is hydrogen or X^3 and Y^3 are both halo or together form a keto group or an

acetal derivative thereof, and X^4 and Y^4 are as defined for X^3 and Y^3, being the same as or different from X^3 and Y^3; or

(f) reduces an imine salt of formula (XIIIa):



(XIIIa)

wherein R and n are as for formula (I), X^- is an anion, A^2 is a chemical bond or a straight or branching, saturated or unsaturated acyclic hydrocarbon radical, which may include a keto group, A^3 is hydrogen or a saturated or unsaturated acyclic hydrocarbon radical, which may include a keto group, with the proviso that A^2 and A^3 together contain no more than 2 carbon atoms.

9. A pharmaceutical formulation of a 1-aryl-alkylimidazole characterised in that it comprises an imidazole according to any one of claims 1 to 6 or prepared by a process according to claim 7 or 8 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor.

10. A pharmaceutical formulation as claimed in claim 9 characterised in that it is in the form of a tablet.

11. A pharmaceutical formulation as claimed in claim 9 characterised in that it is in the form of a parenterally acceptable injectable solution or suspension.

12. A pharmaceutical formulation as claimed in claim 9 characterised in that it is in the form of a capsule.

13. A tablet of 1-(3,4-dimethylbenzyl)imidazole or a pharmaceutically acceptable salt thereof.

14. A tablet as claimed in claim 13 characterised in that it contains from 50 to 500 mg of the imidazole or a pharmaceutically acceptable salt thereof, said amount being the amount of the imidazole base present.

15. A method of preparing a pharmaceutical formulation characterised in that one admixes a 1-arylalkylimidazole or a pharmaceutically acceptable

acid addition salt thereof as defined in claim 1 with a pharmaceutically acceptable carrier thereof.

16. A 1-arylalkylimidazole as defined in any one of claims 1 to 6 or prepared by a process according to claim 7 or 8 or a pharmaceutically acceptable salt thereof, as an active agent for the treatment or prophylaxis of thrombo-embolic disorders of a mammal or mammalian tissue.

17. 1-(3,4-dimethylbenzyl)imidazole or a pharmaceutically acceptable acid addition salt thereof as an active agent in the treatment or prophylaxis of thrombi in a mammal or mammalian tissue.

18. 1-(3,4-dimethylbenzyl)imidazole or a pharmaceutically acceptable acid addition salt thereof as an active agent for the treatment or prophylaxis of myocardial infarction.

19. A pharmaceutical formulation according to any one of claims 9 to 14 as an active agent for the treatment or prophylaxis of a thrombo-embolic disorder in a mammal or mammalian tissue.

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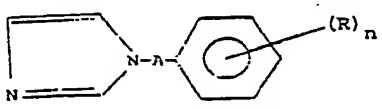
(54) Imidazole derivatives and salts thereof, their synthesis, and intermediates, and pharmaceutical formulations.

(57) The invention relates to 1-arylalkylimidazoles of formula



(I)

in which A is a straight or branched alkylene group of from 1 to 3 carbon atoms, or a straight or branched alkenylene or alkynylene group of 2 or 3 carbon atoms, n is an integer which is at least 1, and the or each R substituent, which when n is greater than 1 may be the same or different, is a saturated alkyl group of from 1 to 4 carbon atoms or an unsaturated alkyl group of from 2 to 4 carbon atoms, with the proviso that when A is unsaturated, R may also be alkoxy of from 1 to 4 carbon atoms; (when n is at least 2) alkylenedioxy of from 1 to 4 carbon atoms; halo; trihalomethyl; hydroxy; carboxyl; a salt of such a carboxyl group; carboalkoxy; carboaryloxy; carboarylalkyloxy; $-NR^6R^7$ or $-CONR^6R^7$, in which R^6 and R^7 may be the same or different and are hydrogen or alkyl of from 1 to 4 carbon atoms; or an acid addition salt of such a 1-arylalkylimidazole.

Methods of preparing these 1-arylalkylimidazoles are disclosed.

The 1-arylalkylimidazoles have pharmacological properties of use in medicine, in particular for the treatment or prophylaxis of thrombo-embolic disorders.

EP 0 003 732 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP. 78 10 1294

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	US - A - 3 927 017 (HEERES - BACKX - MOSTMANS) * Columns 1-4 *	1,7

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 233/56
233/58
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TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 233/56
233/58

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	14-06-1979	DE BUYSER